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(21) International Application Number: PCT/SE99/01277 (22) International Filing Date: 15 July 1999 (15.07.99) (30) Priority Data: 9802574-5 17 July 1998 (17.07.98) SE (71) Applicant (for all designated States except MG US): ASTRA PHARMACEUTICALS LTD. [GB/GB]; Home Park, Kings Langley, Herts. WD4 8DH (GB). (71) Applicant (for MG only): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): GUILLE, Simon [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB). SPRINGTHORPE, Brian [GB/GB]; Astra Charnwood, Bakewell Road, Loughborough, Leics. LE11 5RH (GB). (74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S-151 85 Södertälje (SE).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: NOVEL TRIAZOLO[4,5- <i>d</i>]PYRIMIDINE COMPOUNDS (57) Abstract <p>The invention provides new triazolo[4,5-<i>d</i>]pyrimidine compounds of formula (I), their use as medicaments, compositions containing them and processes for their preparation.</p> <div style="text-align: center;"> <p style="text-align: right;">(I)</p> </div>		

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NOVEL TRIAZOLO[4,5-*d*]PYRIMIDINE COMPOUNDS

The present invention provides new triazolo[4,5-*d*]pyrimidine compounds, their use as medicaments, compositions containing them and processes for their preparation.

5 Platelet adhesion and aggregation are initiating events in arterial thrombosis. Although the process of platelet adhesion to the sub-endothelial surface may have an important role to play in the repair of damaged vessel walls, the platelet aggregation that this initiates can precipitate acute thrombotic occlusion of vital vascular beds, leading to events with high
10 morbidity such as myocardial infarction and unstable angina. The success of interventions used to prevent or alleviate these conditions, such as thrombolysis and angioplasty is also compromised by platelet mediated occlusion or re-occlusion.

A number of converging pathways lead to platelet aggregation. Whatever the initial
15 stimulus, the final common event is a cross linking of platelets by binding of fibrinogen to a membrane binding site, glycoprotein IIb/IIIa (GPIIb/IIIa). The high anti-platelet efficacy of antibodies or antagonists for GPIIb/IIIa is explained by their interference with this final common event. However, this efficacy may also explain the bleeding problems that have been observed with this class of agent. Thrombin can produce platelet aggregation largely
20 independently of other pathways but substantial quantities of thrombin are unlikely to be present without prior activation of platelets by other mechanisms. Thrombin inhibitors such as hirudin are highly effective anti-thrombotic agents, but again may produce excessive bleeding because they function as both anti-platelet and anti-coagulant agents (The TIMI 9a Investigators (1994), *Circulation* **90**, pp. 1624-1630; The Global Use of Strategies to Open
25 Occluded Coronary Arteries (GUSTO) IIa Investigators (1994) *Circulation* **90**, pp. 1631-1637; Neuhaus K.L. et. al. (1994) *Circulation* **90**, pp.1638-1642).

It has been found that ADP acts as a key mediator of thrombosis. A pivotal role for ADP is supported by the fact that other agents, such as adrenaline and 5-hydroxytryptamine (5HT,
30 serotonin) will only produce aggregation in the presence of ADP. The limited anti-thrombotic efficacy of aspirin may reflect the fact that it blocks only one source of ADP which is that released in a thromboxane-dependent manner following platelet adhesion (see e.g. Antiplatelet Trialists' Collaboration (1994), *Br. Med. J.* **308**, pp. 81-106; Antiplatelet Trialists' Collaboration (1994), *Br. Med. J.* **308**, pp.159-168). Aspirin has no effect on
35 aggregation produced by other sources of ADP, such as damaged cells or ADP released under conditions of turbulent blood flow. ADP-induced platelet aggregation is mediated by

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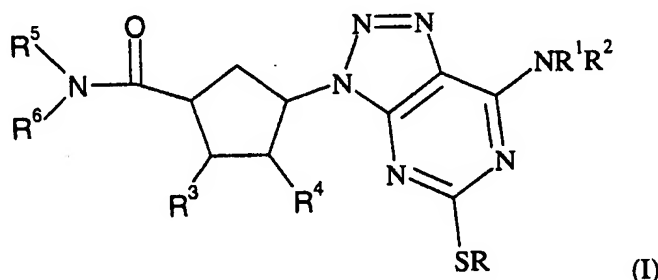
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the P_{2T}-receptor subtype uniquely located on the platelet membrane. Recently it has been shown that antagonists at this receptor offer significant improvements over other anti-thrombotic agents. Accordingly there is a need to find P_{2T}-antagonists as anti-thrombotic agents.

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It has now been found that a series of triazolo[4,5-*d*]pyrimidine derivatives are P_{2T}-receptor antagonists. In a first aspect the invention therefore provides a compound of formula (I):



10

wherein:

R is a C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₈-cycloalkyl, phenyl or a thienyl group, each group being optionally substituted by one or more substituents selected from halogen, OR⁸, NR⁹R¹⁰, SR¹¹ or C₁₋₆ alkyl (itself optionally substituted by one or more halogen atoms);

R¹ is C₁₋₄ alkyl;

R² is C₁₋₈ alkyl optionally substituted by one or more substituents selected from halogen, OR⁸, NR⁹R¹⁰, SR¹¹, C₃₋₈-cycloalkyl, aryl (optionally substituted by one or more alkyl groups and/or halogen atoms), or C₁₋₆-alkyl; or R² is a C₃₋₈-cycloalkyl group optionally substituted by one or more substituents selected from halogen, OR⁸, NR⁹R¹⁰, SR¹¹,

C₁₋₆-alkyl or phenyl (the latter two groups being optionally substituted by one or more substituents selected from halogen, NO₂, C(O)R⁸, OR⁸, SR¹¹, NR¹²R¹³, NR¹⁴COR¹⁵, NR¹⁶SO₂R¹⁷, SO₂NR⁸R⁹, phenyl, OR¹⁸, and C₁₋₆ alkyl which is optionally substituted by one or more halogen atoms);

R³ and R⁴ are both hydroxy;

R⁵ is hydrogen or C₁₋₆ alkyl, and R⁶ is C₁₋₆ alkyl optionally substituted by C₃₋₆-cycloalkyl or R⁶ is C₃₋₆-cycloalkyl or R⁵ and R⁶ together with the nitrogen atom to which they are attached form a 5- to 7-membered saturated ring;

R⁸, R⁹, R¹⁰, R¹¹ and R¹⁴ are independently hydrogen or C₁₋₆ alkyl;

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R^{12} and R^{13} are independently hydrogen, C_{1-6} alkyl or together with the nitrogen atom to which they are attached form a 4- to 8-membered ring;

R^{15} is C_{1-6} alkyl or phenyl;

R^{16} is hydrogen or C_{1-6} alkyl;

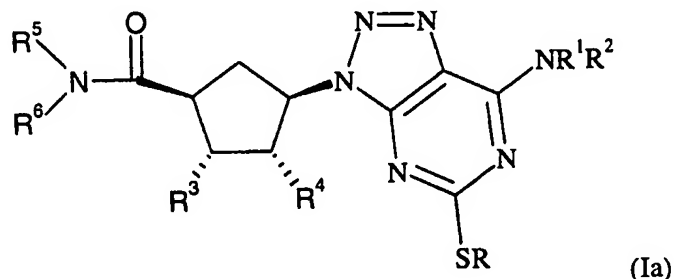
5 R^{17} is C_{1-6} alkyl or phenyl;

R^{18} is phenyl

or a pharmaceutically acceptable salt or solvate thereof.

Alkyl groups, whether alone or as part of another group, can be straight chained or
10 branched. Aryl groups include phenyl and naphthyl groups. Acyl groups include $C(O)C_{1-6}$ alkyl such as acetyl and 1-oxopropyl.

Preferably the compound of formula (I) has the following stereochemistry:



15

Suitably R is a C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-8} -cycloalkyl, phenyl or a thienyl group, each group being optionally substituted by one or more substituents selected from halogen, OR^8 , NR^9R^{10} , SR^{11} or C_{1-6} alkyl (itself optionally substituted by one or more halogen atoms).

20 Preferably R is C_{1-6} alkyl optionally substituted by one or more halogen atoms. More preferably R is methyl or propyl.

Suitably R^1 is C_{1-4} alkyl. More preferably R^1 is methyl.

25 Suitably R^2 is C_{1-8} alkyl optionally substituted by one or more substituents selected from halogen, OR^8 , NR^9R^{10} , SR^{11} , C_{3-8} -cycloalkyl, aryl (optionally substituted by one or more alkyl groups and/or halogen atoms), or C_{1-6} -alkyl; or R^2 is a C_{3-8} -cycloalkyl group optionally substituted by one or more substituents selected from halogen, OR^8 , NR^9R^{10} , SR^{11} , C_{1-6} -alkyl or phenyl (the latter two groups being optionally substituted by one or
30 more substituents selected from halogen, NO_2 , $C(O)R^8$, OR^8 , SR^{11} , $NR^{12}R^{13}$,

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NR¹⁴COR¹⁵, NR¹⁶SO₂R¹⁷, SO₂NR⁸R⁹, phenyl, OR¹⁸, and C₁₋₆ alkyl which is optionally substituted by one or more halogen atoms) where R⁸, R⁹, R¹⁰, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷ and R¹⁸ are as defined above. Preferably R² is C₁₋₆ alkyl or a C₃₋₈-cycloalkyl group optionally substituted by phenyl optionally substituted by one or more substituents selected from halogen, C₁₋₆-alkyl or SO₂NR⁸R⁹. More preferably R² is cyclopropyl optionally substituted by phenyl, 4-chlorophenyl, 3,4-difluorophenyl, 4-(aminosulphonyl)phenyl or 4-(methylaminosulphonyl)phenyl.

Suitably R⁵ is hydrogen or C₁₋₆ alkyl. More preferably R⁵ is hydrogen.

Suitably R⁶ is hydrogen, C₁₋₆ alkyl optionally substituted by hydroxy, halogen or C₃₋₆-cycloalkyl. Preferably R⁶ is hydrogen or C₁₋₆ alkyl optionally substituted by hydroxy or halogen. More preferably R⁶ is hydrogen, ethyl, 2-hydroxyethyl or 2-fluoroethyl.

Particularly preferred compounds of the invention include:

[1S-[1 α ,2 β ,3 β ,4 α (1S*,2R*)]]-N-Ethyl-2,3-dihydroxy-4-[7-[methyl(2-phenylcyclopropyl)amino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]cyclopentanecarboxamide,
 [1S-[1 α ,2 β ,3 β ,4 α (1S*,2R*)]]-N-Ethyl-2,3-dihydroxy-4-[7-[methyl(2-phenylcyclopropyl)amino]-5-(methylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]cyclopentanecarboxamide,
 [1S-[1 α ,2 β ,3 β ,4 α (1S*,2R*)]]-2,3-Dihydroxy-N-(2-hydroxyethyl)-4-[7-[methyl(2-phenylcyclopropyl)amino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]cyclopentanecarboxamide,
 [1S-[1 α ,2 β ,3 β ,4 α (1S*,2R*)]]-2,3-Dihydroxy-4-[7-[methyl(2-phenylcyclopropyl)amino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]cyclopentanecarboxamide,
 [1S-[1 α ,2 β ,3 β ,4 α (1S*,2R*)]]-4-[7-[[2-(3,4-difluorophenyl)cyclopropyl]methylamino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-N-ethyl 2,3-dihydroxycyclopentanecarboxamide,
 [1S-[1 α ,2 β ,3 β ,4 α (1S*,2R*)]]-4-[7-[[2-(4-Chlorophenyl)cyclopropyl]methylamino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-N-ethyl-2,3-dihydroxycyclopentanecarboxamide,

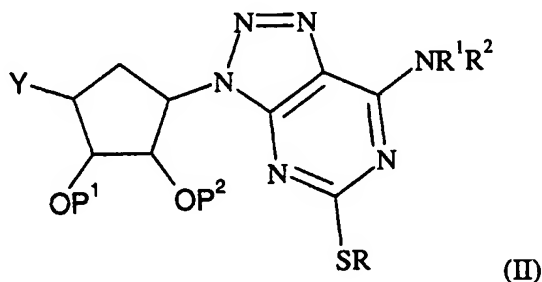
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[1*S*-[1 α ,2 β ,3 β ,4 α (1*S**,2*R**)]]-4-[7-[[2-(4-Aminosulfonylphenyl)cyclopropyl]methylamino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-*N*-ethyl-2,3-dihydroxycyclopentanecarboxamide,
 [1*S*-[1 α ,2 β ,3 β ,4 α (1*S**,2*R**)]]-*N*-Ethyl-2,3-dihydroxy-4-[7-[methyl[2-(4-methylaminosulfonylphenyl)cyclopropyl]amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentanecarboxamide,
 [1*S*-[1 α ,2 β ,3 β ,4 α (1*S**,2*R**)]]-*N*-(2-Fluoroethyl)-2,3-dihydroxy-4-[7-[methyl(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentanecarboxamide
 10 or pharmaceutically acceptable salts or solvates thereof.

According to the invention there is further provided a process for the preparation of a compound of formula (I) which comprises reaction of a compound of formula (II):



where R, R¹ and R² are as defined in formula (I) or are protected derivatives thereof, P¹ and P² are hydrogen or protecting groups and Y is CO₂H, with a compound of formula (III):



where R⁵ and R⁶ are as defined in formula (I), and optionally thereafter in any order:

- converting one or more functional groups into a further functional groups
- removing any protecting groups
- forming a pharmaceutically acceptable salt or solvate.

Examples of suitable groups which each P¹ and P² can independently represent are C₁-6-alkyl (preferably methyl), benzyl, (C₁-6-alkyl)₃Si (preferably trimethylsilyl) and a C(O)C₁-6-alkyl group (preferably acetyl). Preferably the two groups P¹ and P² together

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with the atoms to which they are attached complete a ring, for example the two groups P^1 and P^2 together represent an alkylidene such as methylenidene or, more preferably, isopropylidene, or an alkoxy methylenidene such as ethoxymethylenidene.

- 5 The reaction of compounds of formula (II) and (III) is preferably carried out in the presence of a coupling agent using methods known from peptide synthesis (see M. Bodanszky and A. Bodanszky, *The Practice of Peptide Synthesis*, Springer-Verlag, 1984). Suitable coupling agents include 1,1'-carbonyldiimidazole and dicyclohexylcarbodiimide; the preferred coupling agent is bromo-tris-pyrrolidino-phosphonium hexafluorophosphate or benzotriazole-1-yl-oxy-tris-(dimethylamino)phosphoniumhexafluorophosphate, used in the
10 presence of *N,N*-diisopropylethylamine. The reaction is preferably carried out in *N,N*-dimethylformamide (DMF) or tetrahydrofuran (THF) and preferably at a temperature of from -15° to 120°C, more preferably at a temperature of from 0°C to room temperature.
- 15 Protecting groups can be added and removed using known reaction conditions. The use of protecting groups is fully described in *Protective Groups in Organic Chemistry*, edited by J W F McOmie, Plenum Press (1973), and *Protective Groups in Organic Synthesis*, 2nd edition, T W Greene & P G M Wutz, Wiley-Interscience (1991).
- 20 Alternative methods of activating a compound of formula (II) wherein Y is CO₂H include formation of an acyl halide or an acetic anhydride. Acid anhydrides may be formed by treatment with an acyl halide, such as acetyl chloride in the presence of a base, such as pyridine or by treatment with a dehydrating agent such as acetic acid anhydride or phosphorus pentoxide in an inert solvent. Acyl halides may be formed by treatment of the
25 acid with a halogenating agent, for example P(III), P(V) or S(IV) halides such as phosphorus trichloride. Acyl halides may also be prepared by an exchange reaction of the acid with an acyl halide such as oxalyl bromide. The reactions may be performed in the halogenating agent or acyl halide as solvent or in other inert solvents such as methylene chloride, at a temperature of from 0 to 150°C. Activation is preferably carried out by
30 treatment with oxalyl chloride in dichloromethane at room temperature.

Deprotection can be carried out using methods generally known in the art. For example for groups P^1/P^2 deprotection is preferably carried out as follows:

- 35 (i) where one or both of P^1 and P^2 represent C(O)C₁₋₆-alkyl, these groups can be removed by basic hydrolysis, for example by using a metal hydroxide, preferably an alkali

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metal hydroxide, such as sodium hydroxide or lithium hydroxide, or quaternary ammonium hydroxide in a solvent, such as aqueous ethanol or aqueous tetrahydrofuran, at a temperature of from 10° to 100°C, preferably the temperature is around room temperature; or by acidic hydrolysis using a mineral acid such as HCl or a strong organic acid such as trichloroacetic acid in a solvent such as aqueous 1,4-dioxane;

(ii) where one or both of P^1 and P^2 represent $(C_{1-6}\text{-alkyl})_3Si$, these can be removed by the use of, for example, a fluoride ion source, for example tetra-n-butylammonium fluoride or hydrogen fluoride;

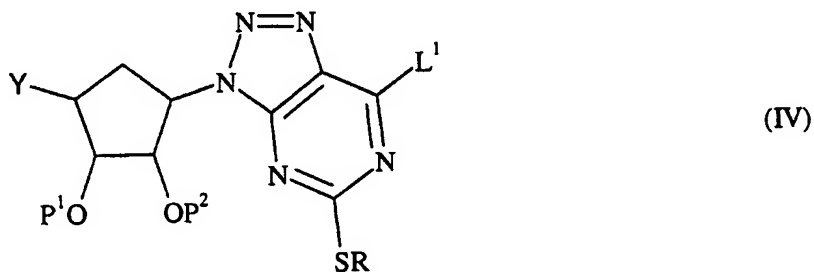
(iii) where one or both of P^1 and P^2 represent a C_{1-6} -alkyl group, these groups can be removed by the use of, for example, boron tribromide;

(iv) where one or both of P^1 and P^2 represent a benzyl group these can be removed by hydrogenolysis using a transition metal catalyst, for example palladium on charcoal, under an atmosphere of hydrogen, at a pressure of from 1 to 5 bar, in a solvent, such as acetic acid; and/or

(v) where both P^1 and P^2 together represent alkylidene or an alkoxy alkylidene, they can be removed by the use of, for example, a mineral or organic acid, preferably by using 2M aqueous hydrochloric acid in methanol/1,4-dioxane or aqueous trifluoroacetic acid at room temperature.

Compounds of formula (III) are commercially available.

A compound of formula (II) wherein Y is CO_2H , $CONR^5R^6$ or $CO_2 R'$ can be prepared by reacting a compound of formula (IV):



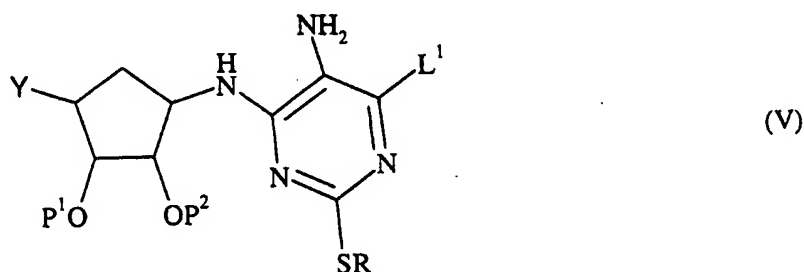
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wherein R, P¹, P², R⁵ and R⁶ are as defined above, L¹ is a leaving group, for example a halogen atom and R' is a C₁₋₆-alkyl or benzyl group, with an amine NHR¹R² or a salt of NHR¹R² wherein R² is as defined above, in the presence of a base. Suitable salts of NHR¹R² include hydrochlorides. Suitable bases include an organic base such as triethylamine or an inorganic base such as potassium carbonate. The amines NHR¹R² can be prepared using procedures described in H Nishiyama *et al*, Bull. Chem. Soc., Jpn., 1995, 68, 1247, P. Newman, Optical Resolution Procedures for Chemical Compounds, Vol. 1, Amines and Related Compounds; Optical Resolution and Information Centre: Manhattan College, Riverdale, NY, 1978, p120, J. Vallgarda *et al*, J. Chem. Soc. Perkin 1, 1994, 461. Certain amines NHR¹R² are novel compounds and form a further aspect of the invention.

A compound of formula (IV) can be prepared by diazotising a compound of formula (V):



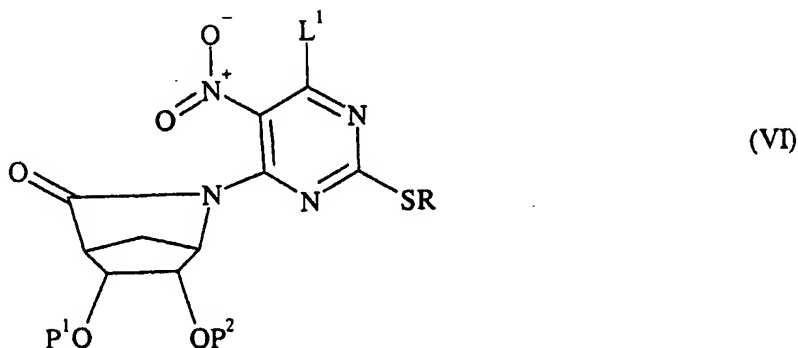
wherein R, Y, L¹, P¹ and P² are as defined above, with a metal nitrite, for example an alkali metal nitrite, especially sodium nitrite in dilute aqueous acid, for example 2M HCl, or with a C₁₋₆-alkyl nitrite in an inert solvent, at a temperature of from -20 to 100°C; preferred conditions are isoamyl nitrite in acetonitrile at 80°C.

A compound of formula (V) where Y is CO₂H can be prepared by reducing and hydrolysing a compound of formula (VI):

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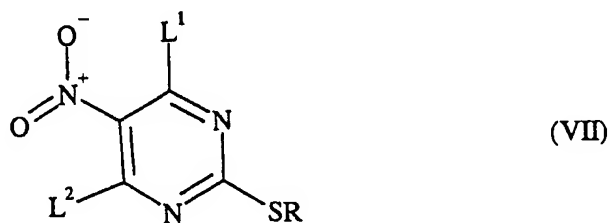


wherein R , L^1 , P^1 and P^2 are as defined above. The reduction may be carried for example by using hydrogenation with a transition metal catalyst at a temperature around room temperature, for example palladium on charcoal under an atmosphere of hydrogen,
 5 preferably at a pressure from 1 to 5 atmospheres, in a solvent, for example ethanol, or by using iron in an acidic solvent such as acetic acid at a temperature of about 100°C.

To prepare a compound of formula (V) wherein Y is CO_2H , following the above reaction,
 10 hydrolysis of the compound derived from the compound of formula (VI) may be performed by using a mineral acid such as HCl or a strong organic acid such as trifluoroacetic acid in a solvent such as aqueous 1,4-dioxane, at a temperature of from 20 to 150°C. Preferably the reduction and hydrolysis are carried out simultaneously using iron in an acidic solvent, for example acetic acid, containing an alkaline earth metal halide, for example calcium
 15 chloride, at a temperature of about 80°C.

To prepare a compound of formula (V) wherein R^9 is C_{1-6} -alkyl or benzyl, the compound of formula (VI) is treated with iron in acetic acid at a temperature of from 50 to 80°C so that the nitro group is reduced. The resulting intermediate is then treated with sodium
 20 borohydride in a mixture of water and C_{1-6} -alkyl alcohol or benzyl alcohol at around room temperature.

A compound of formula (VI) can be prepared by reacting a compound of formula (VII):



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wherein L^1 and R are as defined above and L^2 is a leaving group, for example a halogen atom, wherein L^1 and L^2 are preferably the same, with a compound of formula (VIII):



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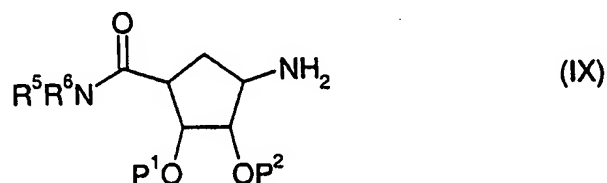
wherein P^1 and P^2 are as defined above, in the presence of a base such as C_{1-6} -alkyl-M or MH wherein M is a metal, for example butyl lithium, in an inert solvent, such as tetrahydrofuran (THF), at a temperature of from -10 to 100°C . Preferably sodium hydride is used in THF at room temperature. Preferably the compound of formula (VIII) has the following stereochemistry such that the above reactions give a compound of formula (Ia):

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15 A compound of formula (VII) may be prepared from 4,6-dihydroxy-2-mercaptopyrimidine by alkylation with RL^3 wherein R is as defined above and L^3 is a suitable leaving group, for example a halogen atom, followed by nitration, whereafter the two alcohols are converted to leaving groups L^1 and L^2 .

20 A compound of formula (V) where Y is CONR^5R^6 can be prepared by reacting a compound of formula (IX):



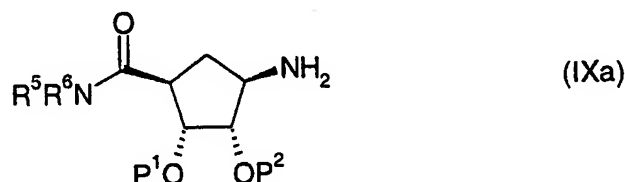
25 with a compound of formula (VII) where P^1 , P^2 , R^1 , R^5 , R^6 , L^1 , and L^2 are as defined above in a suitable solvent such as 1,4-dioxane in the presence of a base such as *N,N*-

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diisopropylethylamine followed by reduction of the nitro group. Compounds of formula (IX) may be prepared using procedures described in WO9528160. Preferably the compound of formula (IX) has the following stereochemistry such that the above reactions give a compound of formula (Ia):



The group SR can be interconverted by oxidation of the sulphur, for example using oxone® or mCPBA, followed by treatment with a compound RSM where R is a different R group and M is a metal such as sodium.

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All novel intermediates form a further aspect of the invention.

Salts of the compounds of formula (I) may be formed by reacting the free acid, or a salt thereof, or the free base, or a salt or a derivative thereof, with one or more equivalents of the appropriate base (for example ammonium hydroxide optionally substituted by C₁-6-alkyl or an alkali metal or alkaline earth metal hydroxide) or acid (for example a hydrohalic (especially HCl), sulphuric, oxalic or phosphoric acid). The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, e.g. water, ethanol, THF or diethyl ether, which may be removed *in vacuo*, or by freeze drying. The reaction may also be a metathetical process or it may be carried out on an ion exchange resin. The non-toxic physiologically acceptable salts are preferred, although other salts may be useful, e.g. in isolating or purifying the product.

20

The compounds of the invention act as P₂₇-receptor antagonists. Accordingly, the compounds are useful in therapy, especially adjunctive therapy, particularly they are indicated for use as: inhibitors of platelet activation, aggregation and degranulation, anti-thrombotic agents or in the treatment or prophylaxis of unstable angina, coronary angioplasty (PTCA), myocardial infarction, perithrombolysis, primary arterial thrombotic complications of atherosclerosis such as thrombotic or embolic stroke, peripheral vascular disease, myocardial infarction with or without thrombolysis, arterial complications due to interventions in atherosclerotic disease such as angioplasty, endarterectomy, stent placement, coronary and other vascular graft surgery, thrombotic complications of surgical

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or mechanical damage such as tissue salvage following accidental or surgical trauma, reconstructive surgery including skin and muscle flaps, conditions with a diffuse thrombotic/platelet consumption component such as disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome, 5 thrombotic complications of septicaemia, adult respiratory distress syndrome, anti-phospholipid syndrome, heparin-induced thrombocytopenia and pre-eclampsia/eclampsia, or venous thrombosis such as deep vein thrombosis, venoocclusive disease, haematological conditions such as myeloproliferative disease, including thrombocythaemia, sickle cell disease; or in the prevention of mechanically-induced platelet activation *in vivo*, such as 10 cardio-pulmonary bypass and extracorporeal membrane oxygenation (prevention of microthromboembolism), mechanically-induced platelet activation *in vitro*, such as use in the preservation of blood products, e.g. platelet concentrates, or shunt occlusion such as in renal dialysis and plasmapheresis, thrombosis secondary to vascular damage/inflammation such as vasculitis, arteritis, glomerulonephritis, inflammatory bowel disease and organ 15 graft rejection, conditions such as migraine, Raynaud's phenomenon, atheromatous plaque formation/progression, vascular stenosis/restenosis and asthma, in which platelet-derived factors are implicated in the disease process.

According to the invention there is further provided the use of a compound according to the 20 invention in the manufacture of a medicament for the treatment of the above disorders. The invention also provides a method of treatment of the above disorders which comprises administering to a patient suffering from such a disorder a therapeutically effective amount of a compound according to the invention.

25 The compounds may be administered topically, e.g. to the lung and/or the airways, in the form of solutions, suspensions, HFA aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, pills, capsules, syrups, powders or granules, or by parenteral administration in the form of sterile parenteral solutions or suspensions, by subcutaneous administration, or by rectal administration in the 30 form of suppositories or transdermally.

The compounds of the invention may be administered on their own or as a pharmaceutical composition comprising the compound of the invention in combination with a pharmaceutically acceptable diluent, adjuvant or carrier. Particularly preferred are 35 compositions not containing material capable of causing an adverse, e.g. an allergic, reaction.

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Dry powder formulations and pressurised HFA aerosols of the compounds of the invention may be administered by oral or nasal inhalation. For inhalation the compound is desirably finely divided.

5

The compounds of the invention may also be administered by means of a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler.

10

One possibility is to mix the finely divided compound with a carrier substance, e.g. a mono-, di- or polysaccharide, a sugar alcohol or another polyol. Suitable carriers include sugars and starch. Alternatively the finely divided compound may be coated by another substance. The powder mixture may also be dispensed into hard gelatine capsules, each containing the desired dose of the active compound.

15

Another possibility is to process the finely divided powder into spheres which break up during the inhalation procedure. This spheronized powder may be filled into the drug reservoir of a multidose inhaler, e.g. that known as the Turbuhaler[®] in which a dosing unit meters the desired dose which is then inhaled by the patient. With this system the active compound with or without a carrier substance is delivered to the patient.

20

The pharmaceutical composition comprising the compound of the invention may conveniently be tablets, pills, capsules, syrups, powders or granules for oral administration; sterile parenteral or subcutaneous solutions, suspensions for parenteral administration or suppositories for rectal administration.

25

For oral administration the active compound may be admixed with an adjuvant or a carrier, e.g. lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, a binder such as gelatine or polyvinylpyrrolidone, and a lubricant such as magnesium stearate, calcium stearate, polyethylene glycol, waxes, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain e.g. gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the tablet may be coated with a suitable polymer dissolved in either a readily volatile organic solvent or an aqueous solvent.

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For the preparation of soft gelatine capsules, the compound may be admixed with e.g. a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the compound using either the above mentioned excipients for tablets, e.g. lactose, saccharose, sorbitol, mannitol, starches, cellulose derivatives or gelatine. Also liquid or semisolid formulations of the drug may be filled into hard gelatine capsules.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example solutions containing the compound, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

The invention is illustrated by the following examples. In the examples the NMR spectra were measured on a Varian Unity Inova 300 or 400 spectrometer and the MS spectra were measured as follows: EI spectra were obtained on a VG 70-250S or Finnigan Mat Incos-XL spectrometer, APCI spectra were obtained on Finnigan Mat SSQ7000 or a Micromass Platform spectrometer. Preparative HPLC separations were generally performed using a Novapak[®], Bondapak[®] or Hypersil[®] column packed with BDSC-18 reverse phase silica. Flash chromatography (indicated in the Examples as (SiO₂)) was carried out using Fisher Matrix silica, 35-70 µm.

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Example 1

5 **[1*S*-[1 α ,2 β ,3 β ,4 α (1*S**,2*R**)]]-*N*-Ethyl-2,3-dihydroxy-4-[7-[methyl(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentanecarboxamide**

a) [3*aR*-(3 α ,4 α ,6 α ,6 α)]-6-[[6-Chloro-5-nitro-2-(propylthio)-4-pyrimidinyl]amino]-*N*-ethyl-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-carboxamide

10

A solution of [3*aR*-(3 α ,4 α ,6 α ,6 α)]-4-amino-*N*-ethyl-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-carboxamide (14.0g) (prepared as described in WO 9528160) in 1,4-dioxane (15ml) was added over 5 minutes to a stirred solution of 4,6-dichloro-5-nitro-2-(propylthio)pyrimidine (32.9g) (prepared as described in WO9703084) in 1,4-dioxane at 15 10°C. *N,N*-Diisopropylethylamine (16ml) was then added and the mixture allowed to warm to room temperature overnight. The reaction mixture was concentrated and the residue purified by chromatography (SiO₂, ether:isohexane 4:1 as eluant) to afford the subtitle compound (17.3g).

20 MS (APCI) 460 (M+H⁺, 100%).

b) [3*aR*-(3 α ,4 α ,6 α ,6 α)]-6-[7-Chloro-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-*N*-ethyl-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-carboxamide

25

To a solution of the product from step a) (32.0g) in acetic acid (300ml) was added iron powder (40.0g). The mixture was stirred at room temperature for 2 hours then filtered through Celite washing with ethyl acetate (3x150ml). The filtrate was concentrated to a volume of 150ml then cooled to 10°C. Sodium nitrite (7.5g) in water (25ml) was added and 30 the solution allowed to warm to room temperature over 40 minutes. Water (200ml) was

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then added and the resultant precipitate collected by filtration, washing with water (100ml) and isohehexane (100ml) afforded the subtitle compound (26.4g).

MS (APCI) 441 (M+H⁺, 100%).

5

c) [3a*R*-[3aα,4α,6α(1*R**,2*S**),6aα]]-*N*-Ethyl-tetrahydro-2,2-dimethyl-6-[7-[methyl(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-4*H*-cyclopenta-1,3-dioxole-4-carboxamide

10 A mixture of the product of step b) (800mg), (1*R*-*trans*)-*N*-methyl-2-phenylcyclopropanamine hydrochloride (prepared as described by C. Kaiser *et al*, J. Org. Chem., **1962**, 27, 768-773, using (1*R*-*trans*)-2-phenylcyclopropanamine, [*R*-(*R**,*R**)]-2,3-dihydroxybutanedioate (1:1), prepared as described by L.A. Mitscher *et al*, J. Med. Chem., **1986**, 29, 2044) (366mg) and *N,N*-diisopropylethylamine (1.5ml) in dichloromethane
15 (50ml) was stirred at room temperature for 16 hours. The reaction mixture was concentrated and the residue purified by chromatography (SiO₂, isohehexane:ethylacetate 2:1 as eluant) to afford the subtitle compound (990mg).

MS (APCI) 552 (M+H⁺, 100%).

20

d) [1*S*-[1α,2β,3β,4α(1*S**,2*R**)]]-*N*-Ethyl-2,3-dihydroxy-4-[7-[methyl(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentanecarboxamide

25 A solution of the product from step c) (275mg) in trifluoroacetic acid (16ml) and water (4ml) was stirred at room temperature for 3 hours. The reaction mixture was concentrated, neutralised with aqueous sodium bicarbonate solution and then extracted with dichloromethane. The organic solution was dried, concentrated and the residue purified by chromatography (SiO₂, dichloromethane:methanol 97:3 as eluant) to afford the title
30 compound (242mg).

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Mpt 154-157°C

MS (APCI) 512 (M+H⁺, 100%).

5

NMR δ H (d₆-DMSO, 90°) 7.58 (1H, s), 7.32-7.17 (5H, m), 4.98 (1H, q), 4.81 (1H, d), 4.66 (1H, d), 4.46 (1H, q), 4.18 (1H, q), 3.16-2.95 (8H, m), 2.77-2.72 (1H, m), 2.41-2.23 (3H, m), 1.66-1.52 (3H, m), 1.47-1.43 (1H, m), 1.04 (3H, t), 0.94 (3H, t).

10 Example 2

[1S-[1 α ,2 β ,3 β ,4 α (1S*,2R*)]]-N-Ethyl-2,3-dihydroxy-4-[7-[methyl(2-phenylcyclopropyl)amino]-5-(methylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]cyclopentanecarboxamide

15

a) [3aR-[3a α ,4 α ,6 α (1R*,2S*),6a α]]-N-Ethyl-tetrahydro-2,2-dimethyl-6-[7-[methyl(2-phenylcyclopropyl)amino]-5-(propylsulfonyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-4H-cyclopenta-1,3-dioxole-4-carboxamide

20 3-Chloroperoxybenzoic acid (85%, 1.0g) was added to a suspension of the product of example 1, step c) (680mg) in ethanol (25ml) and the resulting solution stirred at room temperature for 24 hours. The reaction mixture was concentrated and the residue taken up in ethyl acetate (100ml), washed with 10% aqueous sodium metabisulfite solution (2 x 80ml) and 10% aqueous sodium bicarbonate solution (2x50ml) then dried and
25 concentrated. The residue was purified by chromatography (SiO₂, ethyl acetate: isohexane 1:1 as eluant) to give the subtitle compound (780mg).

MS (APCI) 584 (M+H⁺, 100%).

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b) [3a*R*-[3a α ,4 α ,6 α (1*R**,2*S**),6a α]]-*N*-Ethyl-tetrahydro-2,2-dimethyl-6-[7-[methyl(2-phenylcyclopropyl)amino]-5-(methylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-4*H*-cyclopenta-1,3-dioxole-4-carboxamide

5 Sodium thiomethoxide (300mg) was added to a stirred solution of the product from step a) (390mg) in dry tetrahydrofuran (20ml). The mixture was stirred at room temperature for 24 hours, concentrated and the residue purified by chromatography (SiO₂, isohexane:ethyl acetate 2:1 as eluent) to afford the subtitle compound (329mg).

10 MS (APCI) 524 (M+H⁺, 100%).

c) [1*S*-[1 α ,2 β ,3 β ,4 α (1*S**,2*R**)]]-*N*-Ethyl-2,3-dihydroxy-4-[7-[methyl(2-phenylcyclopropyl)amino]-5-(methylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-cyclopentanecarboxamide

15

The title compound was prepared according to the method of example 1, step d) using the product of step b).

Mpt 152-153°C

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MS (APCI) 484 (M+H⁺, 100%).

NMR δ H (d₆-DMSO, 90°) 7.59 (1H, s), 7.32-7.17 (5H, m), 5.00 (1H, q), 4.83 (1H, d), 4.68 (1H, d), 4.46 (1H, q), 4.19 (1H, q), 3.57 (4H, s), 3.16-2.95 (2H, m), 2.80-2.73 (1H, m),
25 2.40 (3H, s), 2.36-2.20 (3H, m), 1.59-1.52 (1H, m), 1.47-1.41 (1H, m), 1.04 (3H, t).

Example 3

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[1*S*-(1 α ,2 β ,3 β ,4 α (1*S,2*R**))]-2,3-Dihydroxy-*N*-(2-hydroxyethyl)-4-[7-[methyl(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentanecarboxamide**

- 5 **a) [3*aR*-(3 α ,4 α ,6 α ,6 α)]-6-[[5-Amino-6-chloro-2-(propylthio)-4-pyrimidinyl]amino]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-carboxylic acid**

Iron powder (10.0g) was added to a stirred solution of [3*aS*-(3 α ,4 β ,7 β ,7 α)] 5-[6-chloro-5-nitro-2-(propylthio)pyrimidin-4-yl]-tetrahydro-2,2-dimethyl-4,7-methano-1,3-dioxolo[4,5-*c*]pyridin-6(3*aH*)-one (10.0g) (prepared as described in WO9703084) and
10 calcium chloride (4.45g) in ethanol (140ml). The reaction mixture was heated at reflux for 10 minutes then filtered through Celite, washing with hot ethanol. The filtrate was concentrated to afford the subtitle compound (9.3g).

- 15 MS (FAB) 405, 403 ($M+H^+$), 405 (100%).

b) [3*aR*-(3 α ,4 α ,6 α ,6 α)]-6-[7-Chloro-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxole-4-carboxylic acid

20

Isoamyl nitrite (6.02ml) was added to a solution of the product of step a) (9.28g) in acetonitrile (80ml) and the solution heated at 70°C for 1 hour. The cooled reaction mixture was concentrated and the residue purified by chromatography (SiO₂, ethyl acetate:isohexane 2:1 as eluant) to afford the subtitle compound (7.9g).

25

MS (FAB) 416, 414 ($M+H^+$), 414 (100%).

c) [3*aR*-[3 α ,4 α ,6 α (1*R,2*S**),6 α]]-Tetrahydro-2,2-dimethyl-6-[7-[2-phenylcyclopropyl)methylamino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-4*H*-cyclopenta-1,3-dioxole-4-carboxylic acid**

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20

The sub-title compound was prepared according to the method of example 1, step c) using the product of step b).

5 MS (APCI) 525 ($M+H^+$, 100%).

d) [3aR-[3a α ,4 α ,6 α (1R*,2S*),6a α]]-Tetrahydro-*N*-(2-hydroxyethyl)-2,2-dimethyl-6-[7-[methyl(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-4*H*-cyclopenta-1,3-dioxole-4-carboxamide

10

Ethanolamine (0.06ml) was added to a solution of *N,N*-diisopropylethylamine (0.2ml), bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (224mg) and the product of step c) (210mg) in dichloromethane (20ml). The reaction mixture was stirred at room temperature for 4 hours then concentrated. The residue was purified by chromatography (SiO₂, dichloromethane:methanol 98:2 as eluant) to afford the subtitle compound (180mg).

15

MS (APCI) 568 ($M+H^+$, 100%).

e) [1S-[1 α ,2 β ,3 β ,4 α (1S*,2R*)]]-2,3-Dihydroxy-*N*-(2-hydroxyethyl)-4-[7-[methyl(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentanecarboxamide

20

A solution of the product from step d) (470mg) in 1,4-dioxane (5ml) and 2M aqueous hydrochloric acid (5ml) was stirred at room temperature for 16 hours. The reaction mixture was concentrated and the residue taken into ethyl acetate (50ml) and washed with water (2 x 50ml). The organic phase was dried and concentrated and the residue purified by chromatography (SiO₂, dichloromethane:methanol 97:3 as eluent) to afford the title compound (90 mg).

25

30 MS (APCI) 568 ($M+H^+$, 100%).

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NMR δ H (d_6 -DMSO, 90°) 7.59 (1H, t), 7.30-7.18 (5H, m), 4.90 (1H, m), 4.82 (1H, d), 4.68 (1H, d), 4.47 (1H, m), 4.35 (1H, m), 4.19 (1H, m), 3.59 (3H, s), 3.42 (2H, m), 3.20 (2H, m), 3.10-2.90 (2H, m), 2.80 (1H, m), 2.40-2.20 (3H, m), 1.64-1.50 (3H, m), 1.42 (1H, m),
5 0.93 (3H, t).

Example 4

[1S-[1 α ,2 β ,3 β ,4 α (1S*,2R*)]]-2,3-Dihydroxy-4-[7-[methyl(2-
10 phenylcyclopropyl)amino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentanecarboxamide

a) [3aR-[3a α ,4 α ,6 α (1R*,2S*),6a α]]-Tetrahydro-2,2-dimethyl-6-[7-[methyl(2-
phenylcyclopropyl)amino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-
15 4H-cyclopenta-1,3-dioxole-4-carboxamide

The subtitle compound was prepared according to the method of example 3, step d) using the product from example 3, step c) and ammonia.

20 MS (APCI) 568 (M+H⁺, 100%).

b) [1S-[1 α ,2 β ,3 β ,4 α (1S*,2R*)]]-2,3-Dihydroxy-4-[7-[methyl(2-
phenylcyclopropyl)amino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentanecarboxamide

25

The title compound was prepared according to the method of example 3, step e) using the product of step a).

MS (APCI) 484 (M+H⁺, 100%).

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concentrated. The resulting pale yellow solid was treated with TFA (3ml) in water (3ml) and stirred at room temperature for 2 hours. Aqueous sodium bicarbonate was added and the reaction mixture extracted with ethyl acetate. The organic extracts were dried and concentrated to afford the title compound (103mg).

5

Mpt 183-185°C

MS (APCI) 548 (M+H⁺, 100%).

10

NMR δ H (d₆-DMSO) 7.61 (1H, s), 7.33-7.26 (2H, m), 7.10-7.07 (1H, m), 4.96-4.92 (1H, m), 4.83-4.82 (1H, m), 4.70-4.68 (1H, m), 4.48-4.20 (1H, m), 4.19-4.16 (1H, m), 3.55 (4H, s), 3.08-3.04 (4H, m), 3.01-2.93 (1H, m), 2.79-2.73 (1H, m), 2.40-2.21 (3H, m), 1.68-1.57 (3H, m), 1.49-1.44 (1H, m), 1.08 (3H, t), 0.94 (3H, t).

15

Example 6

[1S-[1 α ,2 β ,3 β ,4 α (1S*,2R*)]]-4-[7-[[2-(4-Chlorophenyl)cyclopropyl]methylamino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-N-ethyl-2,3-dihydroxycyclopentanecarboxamide

20

a) (1R-trans)-N-[2-(4-Chlorophenyl)cyclopropyl]acetamide

Acetic anhydride (0.5ml) was added to a solution of (1R-trans)-2-(4-chlorophenyl)cyclopropanamine (0.72g), (prepared as described in WO9905143) in 1M sodium hydroxide (5ml) and stirred for 1 hour. The mixture was extracted with dichloromethane and ethyl acetate (3 times each) and the combined organic extracts were dried and evaporated to afford the subtitle compound (0.92g)

30

MS (APCI) 210,212 (M+H⁺) 210 (100%).

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NMR δ H (d_6 -DMSO) 7.32-7.19 (5H, m), 4.99 (1H, m), 4.82 (1H, d), 4.67 (1H, d), 4.46 (1H, m), 4.20 (1H, m), 3.56 (5H, s), 3.08-2.95 (3H, m), 2.81 (1H, m), 2.42-2.23 (3H, m), 1.66-1.52 (3H, m), 1.45 (1H, m), 0.96 (3H, t).

5 **Example 5**

[1S-[1 α ,2 β ,3 β ,4 α (1S*,2R*)]]-4-[7-[[2-(3,4-difluorophenyl)cyclopropyl]methylamino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-N-ethyl 2,3-dihydroxycyclopentanecarboxamide

10

a) **[3aR-[3a α ,4 α ,6 α (1R*,2S*),6a α]]-6-[7-[2-(3,4-Difluorophenyl)cyclopropylamino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl 4H-cyclopenta-1,3-dioxole-4-carboxamide**

15 A mixture of the products of Example 1, step b) (299mg), (1R-*trans*)-2-(3,4-difluorophenyl)-N-methylcyclopropanamine, [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1) (prepared as described in WO9905143) (238mg) and *N,N*-diisopropylethylamine (0.47ml) in dichloromethane (8ml) were stirred at room temperature for 16 hours. The reaction mixture was dried and concentrated to afford the subtitle compound (330mg).

20 MS (APCI) 574 (M+H⁺, 100%).

b) **[1S-[1 α ,2 β ,3 β ,4 α (1S*,2R*)]]-4-[7-[[2-(3,4-difluorophenyl)cyclopropyl]methylamino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-N-ethyl 2,3-dihydroxycyclopentanecarboxamide**

25

A mixture of the product from step a) (180mg), methyl iodide (59 μ l) and potassium carbonate (130mg) was stirred together in *N,N*-dimethylformamide (2ml) at room temperature for 5 hours. Aqueous ammonium chloride was added and the reaction mixture extracted with ethyl acetate. The organic extracts were washed with water, dried and

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b) (1R-trans)-N-[2-(4-Chlorophenyl)cyclopropyl]-N-methylacetamide

Sodium hydride (228mg, 60% dispersion in oil) was added to a solution of the product
5 from step a) (0.92g) and methyl iodide (0.4ml) in THF (6ml) and the mixture was stirred
for 18 hours. Aqueous ammonium chloride was added and the mixture extracted with
diethyl ether (3 times). The combined organic extracts were dried and evaporated. The
crude product was purified by chromatography (SiO₂, isohexane:ethyl acetate 1:3 as eluent)
to afford the subtitle compound (1.78g).

10

MS (APCI) 224,226 (M+H⁺) 224 (100%).

c) (1R-trans)-2-(4-chlorophenyl)-N-methylcyclopropanamine, hydrochloride

15 A solution of the product from step b) (914mg) in 4M hydrochloric acid (4ml) was heated
under reflux for 8 hours. The solvent was removed *in vacuo* and the residue was
azeotroped with toluene and then triturated with acetone-isohexane to afford the subtitle
compound (850mg)

20 Mpt 150-1°C

MS (APCI) 182 (M-Cl⁻, 100%).

d) [1S-[1 α ,2 β ,3 β ,4 α (1S*,2R*)]]-4-[7-[[2-(4-Chlorophenyl)cyclopropyl]methylamino]-
25 **5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-N-ethyl-2,3-**
dihydroxycyclopentanecarboxamide

A mixture of the products of step c) (120mg), Example 1, step b) (220mg) and *N,N*-
diisopropylethylamine (0.35ml) in dichloromethane (8ml) was stirred at room temperature
30 for 16 hours. The reaction mixture was concentrated and the residue treated with

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trifluoroacetic acid (3ml) in water (3ml). The reaction mixture was stirred at room temperature for 1 hour, neutralised with aqueous sodium bicarbonate solution and extracted with ethyl acetate. The organic extracts were dried, concentrated and the crude product recrystallised (acetonitrile) to afford the title compound (129mg).

5

Mpt 166-168°C

MS (APCI) 546, 548 (M+H⁺), 546 (100%).

10 NMR δ H (d₆-DMSO) 7.93 (1H, m), 7.37-7.35 (2H, m), 7.28-7.25 (2H, m), 5.12-5.10 (1H, m), 4.99-4.93 (2H, m), 4.47-4.40 (1H, m), 4.12-4.09 (1H, m), 3.33 (1H, s), 3.12-3.05 (3H, m), 2.76-2.70 (1H, m), 2.33-2.20 (3H, m), 1.65-1.48 (4H, m), 1.03 (3H, t), 0.95 (3H, t).

15 **Example 7**

[1S-[1 α ,2 β ,3 β ,4 α (1S*,2R*)]]-4-[7-[[2-(4-Aminosulfonylphenyl)cyclopropyl]methylamino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-N-ethyl-2,3-dihydroxycyclopentanecarboxamide

20

a) (1R-trans)-N-2-Phenylcyclopropylacetamide

The subtitle compound was prepared as described for Example 6, step a) using (1R-trans)-2-phenylcyclopropanamine, [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1) (prepared as described by L.A. Mitscher *et al*, J. Med. Chem., 1986, 29, 2044).

25

MS (APCI) 176 (M+H⁺, 100%)

b) (1R-trans)-N-Methyl-N-2-phenylcyclopropylacetamide

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The subtitle compound was prepared as described for Example 6, step b) using the product of step a).

MS (APCI) 190 ($M+H^+$, 100%)

5

c) (1*S-trans*)-4-[2-(*N*-methylacetylamino)cyclopropyl]benzenesulfonylchloride

Chlorosulfonic acid (8ml) was slowly added to the product from step b) (2.17g) at -78°C and then allowed to warm to 20°C and stirred for 20 hours. The mixture was poured into
10 ice-water (100ml) and extracted with ethyl acetate (3 times). The combined organic extracts were dried and evaporated to afford the subtitle compound (3.48g).

MS (APCI) 288, 290 ($M+H^+$), 288 (100%)

15

d) (1*S-trans*)-*N*-[2-(4-Aminosulfonylphenyl)cyclopropyl]-*N*-methylacetamide

A mixture of the product from step c) (1.74g) in conc. aqueous ammonia (5ml) was heated at 50°C for 1.5 hours. The mixture was extracted with ethyl acetate (8 times) and the combined organic layers were dried and evaporated. The crude product purified by
20 chromatography (SiO_2 , dichloromethane:methanol 14:1 as eluent) to afford the subtitle compound (1.30g).

NMR δ_H (d_6 -DMSO) 7.73 (2H, d), 7.32 (2H, d), 7.25 (2H, s), 3.03-2.98 (1H, m), 2.84 (3H, s), 2.44-2.37 (1H, m), 2.00 (3H, s), 1.56-1.41 (2H, m).

25

e) (1*S-trans*)-4-[2-(Methylamino)cyclopropyl]benzenesulfonamide, hydrochloride

A solution of the product from step d) (1.19g) in 4M HCl (7ml) was heated under reflux for 6 hours. After cooling the precipitate was collected, washed with ether and dried to afford
30 the subtitle compound (782mg).

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Mpt 173-4°C.

MS (APCI) 227 (M-Cl⁻, 100%).

5

f) [1S-[1 α ,2 β ,3 β ,4 α (1S*,2R*)]]-4-[7-[[2-(4-Aminosulfonylphenyl)cyclopropyl)methylamino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-N-ethyl-2,3-dihydroxycyclopentanecarboxamide

10 A mixture of the product from step e) (144mg), the product from Example 1 step b) (219mg) and *N,N*-diisopropylethylamine (0.21ml) in THF (5ml) was stirred at room temperature for 16 hours. Aqueous sodium dihydrogen phosphate solution was added, the mixture was extracted with ethyl acetate (3 times). The combined organic layers were dried, evaporated and the residue dissolved in acetic acid (4ml) and water (1ml) and heated
15 at 80°C for 3 hours. The solvent was removed *in vacuo*, aqueous ammonia added and re-evaporated. The residue was purified by chromatography (SiO₂, dichloromethane:methanol 11:1 as eluent) and the crude product triturated with ether to afford the title compound (224mg).

20 Mpt 132-5°C.

MS (APCI) 591 (M+H⁺, 100%).

NMR δ H (d₆-DMSO) 7.92 (1H, t), 7.75 (2H, d), 7.42 (2H, d), 7.31 (2H, s), 4.98 (1H, q),
25 4.46-4.41 (1H, m), 4.11 (1H, t), 4.00-2.90 (9H, m), 3.09 (2H, quintet), 2.72 (1H, dq), 2.38-2.18 (2H, m), 1.80-1.44 (4H, m), 1.02 (3H, t), 0.91 (3H, s).

Example 8

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[1S-[1 α ,2 β ,3 β ,4 α (1S*,2R*)]]-N-Ethyl-2,3-dihydroxy-4-[7-[methyl[2-(4-methylaminosulfonylphenyl)cyclopropyl]amino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]cyclopentanecarboxamide

5 a) (1S-*trans*)-N-Methyl-N-[2-(4-methylaminosulfonylphenyl)cyclopropyl]acetamide

A mixture of the product from Example 7, step c) (1.74g) in 40% aqueous methylamine (6ml) was heated at 50°C for 1.5 hours. The mixture was extracted with ethyl acetate (7 times). The combined organic extracts were dried and evaporated and the crude product
10 purified by chromatography (SiO₂, dichloromethane:methanol 11:1 as eluent) to afford the subtitle compound (1.40g).

NMR δ H (d₆-DMSO) 7.67 (2H, d), 7.37 (2H, d), 7.31 (1H, s), 3.07-2.99 (1H, m), 2.83 (3H, s), 2.43-2.38 (4H, m), 2.00 (3H, s), 1.58-1.41 (2H, m).

15

b) (1S-*trans*)-N-Methyl-4-[2-(methylamino)cyclopropyl]benzenesulfonamide hydrochloride

A solution of the product from step a) (1.37g) in 4M HCl (7ml) was heated under reflux for
20 8h. After cooling the solvent was removed *in vacuo* and the residue crystallised (isopropanol) to afford the subtitle compound (1.01g).

Mpt 174-5°C.

25 MS (APCI) 241 (M-Cl⁻, 100%).

c) [1S-[1 α ,2 β ,3 β ,4 α (1S*,2R*)]]-N-Ethyl-2,3-dihydroxy-4-[7-[methyl[2-(4-methylaminosulfonylphenyl)cyclopropyl]amino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]cyclopentanecarboxamide

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The title compound was prepared according to the method of Example 7, step f) using the product from step b) and the product from Example 1, step b).

Mpt 124-6°C.

5

MS (APCI) 605 (M+H⁺, 100%).

NMR δ H (d₆-DMSO) 7.91 (1H, t), 7.70 (2H, d), 7.45 (2H, d), 7.39 (1H, q), 5.05 (1H, s), 4.97 (1H, q), 4.44 (1H, m), 4.11 (1H, q), 4.00-2.85 (7H, m), 3.12 (2H, quintet), 2.72 (1H, dt), 2.43-2.18 (3H, m), 2.41 (3H, d), 1.80-1.43 (4H, m), 1.03 (3H, t), 0.87 (3H, s).

10

Example 9

15 . [1S-[1 α ,2 β ,3 β ,4 α (1S*,2R*)]]-N-(2-Fluoroethyl)-2,3-dihydroxy-4-[7-[methyl(2-phenylcyclopropyl)amino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]cyclopentanecarboxamide

20 2-Fluoroethylamine hydrochloride (23mg) was added to a solution of *N,N*-diisopropylethylamine (110 μ l), 1-hydroxybenzotriazole hydrate (39mg), 2-(1H-benzotriole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (81mg) and the product of Example 3, step c) (110mg) in *N,N*-dimethylformamide (10ml). The reaction mixture was stirred at room temperature for 1.5 hours, poured into 2N HCl and the resulting precipitate
25 washed with water and dried to afford a white solid. Trifluoroacetic acid (3ml) in water (2ml) were added to this solid in methanol (2ml) and the reaction mixture stirred at room temperature for 2 hours. The reaction mixture was basified with 2N potassium carbonate solution and extracted with ethyl acetate. The organic extracts were washed with water, dried and concentrated and the crude product purified by chromatography (SiO₂,
30 dichloromethane:methanol 98:2 as eluent) to afford the title compound (74mg).

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Mpt 141-143°C

MS (APCI) 530 (M+H⁺, 100%).

5

NMR δ H (d₆-DMSO) 8.20-8.18 (1H, m), 7.34-7.20 (5H, m), 5.14-5.12 (1H, m), 5.02-4.98 (2H, m), 4.54-4.50 (1H, m), 4.56-4.43 (1H, m), 4.38-4.34 (1H, m), 4.14-4.13 (1H, m), 3.45-3.42 (2H, m), 3.19-2.89 (4H, m), 2.83-2.81 (2H, m), 2.35-2.25 (2H, m), 1.59-1.54 (3H, m), 0.93 (3H, t).

10

BIOLOGICAL ASSAYS

Washed Platelet Preparation

15 Human venous blood (100 ml), obtained from a healthy volunteer, was divided equally between 3 tubes, each containing 3.2% trisodium citrate (4 ml) as an anti-coagulant. The tubes were centrifuged for 15 minutes at 240g to obtain platelet-rich plasma (PRP) to which prostacyclin (PGI₂ 300 ng·ml⁻¹) was added to stabilize platelets during the washing procedure. Red cell-free PRP was obtained by centrifugation for 10 minutes at 125g and, following
20 further centrifugation for 15 minutes at 640g, the supernatant was discarded and the platelet pellet in each tube resuspended in modified, calcium-free, Tyrodes (CFT) solution (10 ml, composition: NaCl, 137.0 mM; NaHCO₃, 11.9 mM; NaH₂PO₄, 0.4 mM; KCl, 2.7 mM; MgCl₂, 1.1 mM and dextrose, 5.55 mM), gassed with 95% O₂/5% CO₂ and maintained at 37°C. Following addition of PGI₂ (300 ng·ml⁻¹), the pooled suspension was centrifuged once
25 more for 15 minutes at 640g. The supernatant was discarded and the platelets resuspended in CFT to give a final platelet count of 200-250 × 10³·μl⁻¹. The platelets were used within 30 minutes for radioligand binding studies.

Binding Assays

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Binding assays were performed in 96-well plates, with each well containing aliquots of CFT (250 μ l) consisting of 0.1 μ Ci [125 I]-[1*S*-[1 α ,2 β ,3 β ,4 α (*E*)]-2,3-dihydroxy-4-[7-(3-iodo-prop-2-enylamino)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentanecarboxylic acid (50 μ l, final concentration 0.18 nM) and washed platelets at a concentration of $200\text{--}250 \times 10^3 \cdot \mu\text{l}^{-1}$ (200 μ l, final concentration $160\text{--}200 \times 10^3 \cdot \mu\text{l}^{-1}$). The plates were incubated for 30 minutes at room temperature on a plate shaker (Stuart scientific; model S01, setting 6) prior to terminating the reactions by filtration. Filtration was performed using either a MACHIII cell harvester with 2 x 2 second wash periods (with CFT) on to Whatman GF/B filter plates or a Wallac cell harvester using glass fibre printed filtermats type A, with a 7 second wash time (with CFT). The resultant filterplates were then, in the case of the MACHIII, sealed and Microscint 20 (50 ml) added prior to determination of [125 I] levels by scintillation counting on a Packard Topcounter or, in the case of the Wallac filtermats, the individual wells were punched into vials for determination of [125 I] in a Riastar gamma counter.

Non-specific binding was determined in the presence of the standard P2Y_{ADP} antagonist, 2-propylthio-D- β , γ -dichloromethylene ATP (10 μ M), as described by Humphries et al., Br. J. Pharmacology (1995), 115, 1110-1116. All compounds were tested in duplicate over the appropriate concentration range with solvent controls in parallel.

Data Analysis

Results were expressed as specific binding in CPM and were calculated by subtracting the non-specific binding from the total binding achieved at each concentration. For each compound, a binding affinity (IC₅₀) was calculated by linear interpolation of the concentration/inhibition curve, using the software package Excel. The IC₅₀ value being the concentration at which a 50% reduction in specific binding of [125 I]-[1*S*-[1 α ,2 β ,3 β ,4 α (*E*)]-2,3-dihydroxy-4-[7-(3-iodo-prop-2-enylamino)-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentanecarboxylic acid was achieved. Results were reported as pKi

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values which are equal to the negative logarithm of the IC_{50} (pIC_{50}) in this system (Cheng Prusoff).

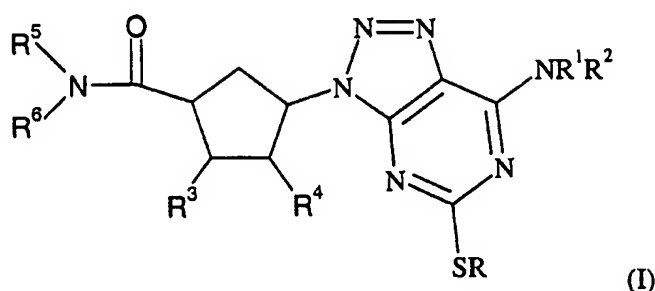
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Claims

1. A compound of formula (I)



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wherein:

- R is a C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₈-cycloalkyl, phenyl or a thienyl group, each group being optionally substituted by one or more substituents selected from halogen, OR⁸, NR⁹R¹⁰, SR¹¹ or C₁₋₆ alkyl (itself optionally substituted by one or more halogen atoms);
- R¹ is C₁₋₄ alkyl;
- R² is C₁₋₈ alkyl optionally substituted by one or more substituents selected from halogen, OR⁸, NR⁹R¹⁰, SR¹¹, C₃₋₈-cycloalkyl, aryl (optionally substituted by one or more alkyl groups and/or halogen atoms), or C₁₋₆-alkyl; or R² is a C₃₋₈-cycloalkyl group optionally substituted by one or more substituents selected from halogen, OR⁸, NR⁹R¹⁰, SR¹¹, C₁₋₆-alkyl or phenyl (the latter two groups being optionally substituted by one or more substituents selected from halogen, NO₂, C(O)R⁸, OR⁸, SR¹¹, NR¹²R¹³, NR¹⁴COR¹⁵, NR¹⁶SO₂R¹⁷, SO₂NR⁸R⁹, phenyl, OR¹⁸, and C₁₋₆ alkyl which is optionally substituted by one or more halogen atoms);
- R³ and R⁴ are both hydroxy;
- R⁵ is hydrogen or C₁₋₆ alkyl, and R⁶ is C₁₋₆ alkyl optionally substituted by C₃₋₆-cycloalkyl or R⁶ is C₃₋₆-cycloalkyl or R⁵ and R⁶ together with the nitrogen atom to which they are attached form a 5- to 7-membered saturated ring;
- R⁸, R⁹, R¹⁰, R¹¹ and R¹⁴ are independently hydrogen or C₁₋₆ alkyl;
- R¹² and R¹³ are independently hydrogen, C₁₋₆ alkyl or together with the nitrogen atom to which they are attached form a 4- to 8-membered ring;
- R¹⁵ is C₁₋₆ alkyl or phenyl;
- R¹⁶ is hydrogen or C₁₋₆ alkyl;
- R¹⁷ is C₁₋₆ alkyl or phenyl;
- R¹⁸ is phenyl

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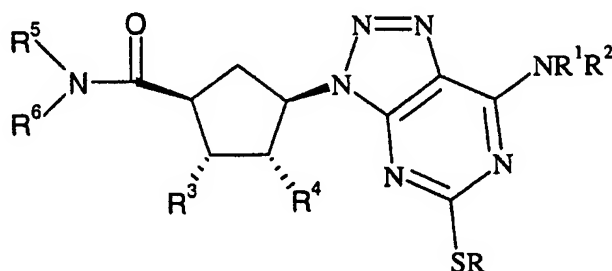
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or a pharmaceutically acceptable salt or solvate thereof.

2. A compound according to claim 1 in which R is methyl or propyl.
3. A compound according to claim 1 or 2 in which R¹ is methyl.
4. A compound according to any one of claims 1 to 3 in which R² is cyclopropyl optionally substituted by phenyl, 4-chlorophenyl, 3,4-difluorophenyl, 4-(aminosulphonyl)phenyl or 4-(methylaminosulphonyl)phenyl.
5. A compound according to any one of claims 1 to 4 in which R⁵ is hydrogen and R⁶ is hydrogen or C₁₋₆ alkyl optionally substituted by hydroxy or fluorine.
6. A compound according to any one of claims 1 to 5 with the following stereochemistry



7. A compound according to claims 1 to 6 which is:
 [1S-[1 α ,2 β ,3 β ,4 α (1S*,2R*)]]-N-Ethyl-2,3-dihydroxy-4-[7-[methyl(2-phenylcyclopropyl)amino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]cyclopentanecarboxamide,
 [1S-[1 α ,2 β ,3 β ,4 α (1S*,2R*)]]-N-Ethyl-2,3-dihydroxy-4-[7-[methyl(2-phenylcyclopropyl)amino]-5-(methylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]cyclopentanecarboxamide,
 [1S-[1 α ,2 β ,3 β ,4 α (1S*,2R*)]]-2,3-Dihydroxy-N-(2-hydroxyethyl)-4-[7-[methyl(2-phenylcyclopropyl)amino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]cyclopentanecarboxamide,
 [1S-[1 α ,2 β ,3 β ,4 α (1S*,2R*)]]-2,3-Dihydroxy-4-[7-[methyl(2-phenylcyclopropyl)amino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]cyclopentanecarboxamide,

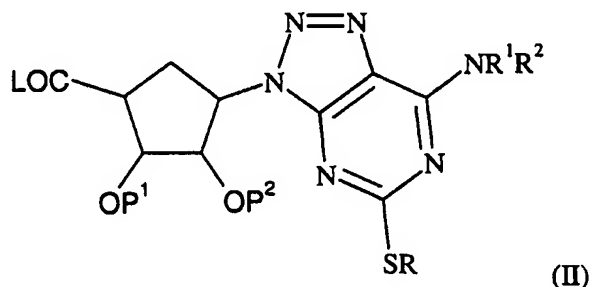
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- [1*S*-[1 α ,2 β ,3 β ,4 α (1*S**,2*R**)]]-4-[7-[[2-(3,4-difluorophenyl)cyclopropyl]methylamino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-*N*-ethyl 2,3-dihydroxycyclopentanecarboxamide,
- [1*S*-[1 α ,2 β ,3 β ,4 α (1*S**,2*R**)]]-4-[7-[[2-(4-Chlorophenyl)cyclopropyl]methylamino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-*N*-ethyl-2,3-dihydroxycyclopentanecarboxamide,
- [1*S*-[1 α ,2 β ,3 β ,4 α (1*S**,2*R**)]]-4-[7-[[2-(4-Aminosulfonylphenyl)cyclopropyl]methylamino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-*N*-ethyl-2,3-dihydroxycyclopentanecarboxamide,
- [1*S*-[1 α ,2 β ,3 β ,4 α (1*S**,2*R**)]]-*N*-Ethyl-2,3-dihydroxy-4-[7-[methyl[2-(4-methylaminosulfonylphenyl)cyclopropyl]amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentanecarboxamide,
- [1*S*-[1 α ,2 β ,3 β ,4 α (1*S**,2*R**)]]-*N*-(2-Fluoroethyl)-2,3-dihydroxy-4-[7-[methyl(2-phenylcyclopropyl)amino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentanecarboxamide or pharmaceutically acceptable salts or solvates thereof.

8. A pharmaceutical composition comprising a compound according to any one of claims 1 to 7 in combination with a pharmaceutically acceptable diluent, adjuvant or carrier.
9. A compound according to any one of claims 1 to 8 for use in therapy.
10. A process for the preparation of a compound of formula (I) which comprises;
(a) reaction of a compound of formula (II):



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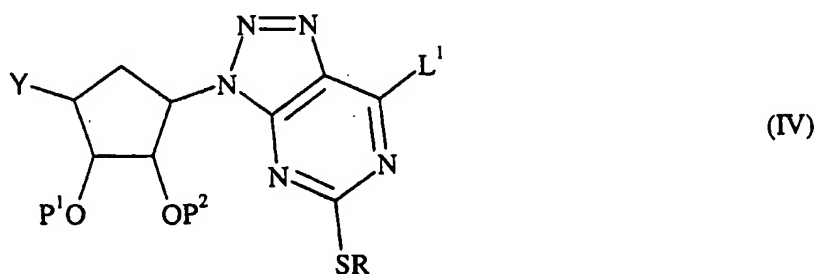
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where R, R¹ and R² are as defined in formula (I) or are protected derivatives thereof, P¹ and P² are hydrogen or protecting groups and L is a leaving group, with a compound of formula (III):



where R¹ and R² are as defined in formula (I), or
(b) reacting a compound of formula (IV):



wherein Y is CO₂H, CO₂ R' or CONR⁵R⁶ and R, R⁵, R⁶, P¹ and P² are as defined above and L¹ is a leaving group and R' is a C₁₋₆-alkyl or benzyl group, with an amine NHR¹R² or a salt of NHR¹R² wherein R² is as defined above

15 and optionally thereafter (a) or (b) and in any order:

- converting one or more functional groups into a further functional groups
- removing any protecting groups
- forming a pharmaceutically acceptable salt or solvate.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 99/01277

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 487/04, A61K 31/505, A61K 31/41 // (C07D 487/04, 249:00, 239:00)
 According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9828300 A1 (ASTRA PHARMACEUTICALS LTD.), 2 July 1998 (02.07.98), page 12, line 1 - page 14, line 24; page 19, line 25 - line 36; page 24, line 5 - line 15, page 38, line 14 - line 36; page 60, line 1 - line 26; page 65, line 9 - page 66, line 26 --	1-10
A	WO 9703084 A1 (ASTRA PHARMACEUTICALS LTD.), 30 January 1997 (30.01.97) --	1-10
P,X	WO 9905142 A1 (ASTRA PHARMACEUTICALS LTD.), 4 February 1999 (04.02.99), page 35, line 28 - page 36, line 12, the claims -- -----	1-10

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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Date of the actual completion of the international search

20 October 1999

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INTERNATIONAL SEARCH REPORT

Information on patent family members

28/09/99

International application No.

PCT/SE 99/01277

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9828300 A1	02/07/98	AU 5501598 A SE 9604787 D SE 9604788 D	17/07/98 00/00/00 00/00/00
WO 9703084 A1	30/01/97	AU 699034 B AU 6375196 A BR 9609467 A CA 2226758 A CN 1195353 A CZ 9800025 A EP 0840740 A GB 9514074 D HU 9802448 A IL 122814 D JP 11508914 T NO 980080 A NZ 312258 A PL 324396 A SK 2398 A US 5747496 A GB 9520311 D GB 9522837 D	19/11/98 10/02/97 02/03/99 30/01/97 07/10/98 12/08/98 13/05/98 00/00/00 28/05/99 00/00/00 03/08/99 06/03/98 30/08/99 25/05/98 11/01/99 05/05/98 00/00/00 00/00/00
WO 9905142 A1	04/02/99	AU 8370598 A SE 9702772 D	16/02/99 00/00/00

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